TRANSPLANTATION

Transplantation of organs, tissues, and cells has become a powerful mode of treatment for dozens of life-threatening diseases affecting millions of Americans. Today, doctors routinely transplant more than 25 different organs and tissues to treat kidney failure, type 1 diabetes, leukemia, end-stage pulmonary disease, liver disorders, cardiovascular disease, and many other disorders.

Two major impediments to successful transplantation remain, however. The first of these is immune system rejection. Recent research advances have provided a much clearer understanding of the immune mechanisms that cause graft rejection. These insights have in turn led to better therapies to suppress the immune system, and thereby allow a graft to survive and function. As a result, 1-year graft survival rates have increased for all organs and tissues, and in many cases now exceed 80 percent. But despite this improvement, long-term graft survival rates have not increased nearly as much.

The second barrier to wider use of transplantation is a critical shortage of donor organs and tissues. Nationwide, there are more than 87,000 candidates on waiting lists for organ transplantation: 59,737 for kidneys; 17,462 for livers; 4,076 for pancreas or combined kidney/pancreas transplants; 3,576 for hearts or heart-lung transplants; and 3,946 for lung transplants.[62] This demand far outstrips the supply of donor organs in the United States. In 2003, 13,280 individuals were organ donors; for the third consecutive year, most of these were living donors.[63] Unfortunately, many candidates die while awaiting a suitable organ.

Immune-Mediated Graft Rejection

To further improve both short- and long-term graft survival, the NIAID Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad portfolio of basic research in transplantation immunology, as well as preclinical evaluation and clinical trials of promising post-transplant therapies. The major goals of DAIT's transplantation research program are to understand the pathways whereby the immune system recognizes transplanted organs, tissues, and cells; characterize the cellular and molecular components of acute rejection and chronic graft failure; evaluate novel therapies for treating rejection and prolonging graft survival in preclinical models; develop and implement strategies for immune tolerance induction; and conduct clinical trials of new therapies to improve graft survival, while minimizing the toxic side effects of immunosuppressive drugs.

Kidney transplantation, which is the preferred therapy for end-stage renal disease, accounts for 59 percent of all solid organ transplants. In fiscal year (FY) 2003, NIAID renewed the Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) program, first established in 1994. The goals of CCTPT are to support multicenter clinical trials of new ways to prevent graft rejection in pediatric kidney transplant patients, evaluate changes in drug regimens intended to limit side effects of immunosuppression, and assess pre-transplant immunotherapies. Ongoing CCTPT clinical trials include an evaluation of the immunosuppressive drug sirolimus for chronic graft failure, and a study of the effects of steroid withdrawal in pediatric transplant recipients. CCTPT also conducts immunological studies to determine how these various interventional approaches affect the immune system.

In FY 2004, NIAID collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute to establish a clinical consortium intended to improve the success of organ transplants. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes, as well as responses to post-transplant therapy; to develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and to

test the safety and effectiveness of new, less toxic immunosuppressive drugs.

NIAID and NIDDK also cooperatively established the Genomics of Transplantation Cooperative Research Program to support interdisciplinary, large-scale genomic studies in clinical transplantation. The goals of the program are to understand the genetic factors that affect immune-mediated graft rejection and to provide a rational basis for the development of more effective strategies for long-term graft survival.

In FY 2003, NIAID launched a clinical trial of dietary supplements in kidney transplant recipients. Previous data suggested that extra arginine and omega-3 fatty acids in the diet might reduce the incidence of post-transplant infections, duration of hospital stays, and frequency of acute rejection episodes. The current trial is investigating the tolerability and safety of this dietary regimen, as well as its effect on post-transplant health. If it proves effective, this intervention could reduce healthcare costs and increase quality of life for transplant recipients.

Patients with HIV infection are at high risk for end-stage organ disease. Before the advent of highly active antiretroviral therapy (HAART), people with HIV were generally not considered for transplants because of their poor prognosis. HAART, however, has improved the outlook for HIV-positive patients so that many more HIV-positive patients with end-stage kidney and liver disease are potential transplant candidates. In FY 2003, DAIT and the NIAID Division of AIDS launched a clinical trial of the safety and efficacy of kidney and liver transplantation in patients with HIV.

Induction of Immune Tolerance

The drug regimens that suppress a patient's immune system usually can prevent graft rejection, but they also cause serious side effects such as infections and malignancies. Transplant immunologists, therefore, hope to develop treatments that can both reduce these risks and improve graft survival. One promising alternative is to selectively modify the immune response to establish tolerance to the graft while leaving protective immune responses intact. In collaboration with NIDDK, DAIT in FY 2002 renewed and expanded the Nonhuman Primate Immune Tolerance Cooperative Study Group. This program evaluates novel regimens intended to induce transplant tolerance in animal models. Scientists working in the study group have already demonstrated that kidney and islet transplant patients given tolerogenic regimens have increased long-term graft acceptance. In FY 2005, the program will be expanded to include heart and lung transplantation. To accelerate the research conducted through this program, DAIT also supports breeding colonies of rhesus and cynomolgus monkeys.

With cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), NIAID supports the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. This network clinically evaluates tolerance-inducing therapies for many immune-mediated disorders, including rejection of transplanted organs, tissues, and cells. ITN also conducts studies on the underlying mechanisms of these approaches and develops new ways to measure the induction, maintenance, and loss of immune tolerance in humans. Since its inception, ITN has established a variety of state-of-the-art core facilities, initiated more than 18 clinical protocols, and funded several basic science studies of the mechanisms of induced immune tolerance. More information on ITN is available at *www.immunetolerance.org*.

Shortage of Donor Organs

The number of organ transplants performed in the United States has increased dramatically, from 12,619 in 1988 to 25,466 in 2003.[64] These numbers would be even higher if more

donor organs were available; the waiting list for transplants has quadrupled since 1988. DAIT is addressing this problem by supporting efforts to improve donor registries that identify potential donors and by developing educational initiatives to increase public understanding of organ donation, especially among minority populations.

In collaboration with several NIH Institutes and Centers and the JDRF, NIAID supports the International Histocompatibility Working Group (IHWG). The IHWG is a network of more than 200 laboratories in more than 70 countries that collects and shares data on the human leukocyte antigen (HLA) gene complex, which determines the compatibility of donor organs and tissues. The goals of this program are to improve histocompatibility testing, find HLA types that are associated with autoimmune diseases, and improve donor-recipient matching for hematopoietic stem cell (HSC) transplantation. IHWG investigators have joined forces with HSC transplant centers to develop an international database of transplantation outcomes and donor–recipient HLA genotypes. This effort will help to determine optimal matching criteria for HSC transplants between unrelated people and increase access to this therapy for ethnically diverse populations. In addition, IHWG researchers are working to identify single nucleotide polymorphisms (SNPs) in immune-response genes. SNP variations may account for the increased susceptibility of certain individuals or groups to immune-mediated diseases. To date, SNP data have been gathered for more than 100 genes related to immune responses.

The use of nonhuman organs, tissues, or cells in human transplantation, called xenotransplantation, is another strategy DAIT is pursuing to increase the supply of transplantable organs and tissues. The potential of xenotransplantation, however, is severely limited by the violent response of the human immune system to nonhuman tissues; concerns have also been expressed that infectious agents might inadvertently be introduced from animal donors into humans. DAIT-supported xenotransplantation research focuses on increasing our understanding of the human immune response to antigens present on cells from nonhuman species, and on the development of methods for rapid identification and treatment of any infectious diseases that might be caused by organisms present in animal donor tissue.

With each advance in transplantation, a new set of challenges emerges. The challenges facing transplantation are improving long-term graft survival, establishing long-term tolerance without immunosuppressive drugs, and reducing lengthy transplant waiting lists. NIAID's basic and clinical research programs in transplantation are committed to meeting these challenges.